

EHRlich VERSUS SYPHILIS

AS IT APPEARED TO

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It is appropriate that in the month which, a hundred years ago, saw the birth of Paul Ehrlich, scientific, particularly medical, periodicals should devote some of their space to reminding their readers of the service which his life-work rendered to mankind. To anyone who has read a good biography of Ehrlich it must be difficult to think of any scientist whose contributions to the prevention and treatment of many diseases have been so great as his.

By desire of the Editor of this periodical the present article will chiefly relate my earliest experiences with the product of Ehrlich's activities in only one field—perhaps the most important—the arsenical compounds which, beginning with “606”, the Ehrlich-Hata remedy, or Salvarsan in 1910, over-worked the words “miracle” and “miraculous” in that year, and began a revolution in the treatment of syphilis which even before the appearance of penicillin had made it one of the most manageable diseases afflicting mankind.

To appreciate the difference which Ehrlich's work in this branch of medical science made, one should know something of the outlook for a patient infected with syphilis before we had the help of his arsenical remedies.

Of course in general literature, notably in Shakespeare's plays, there has been plenty to justify the traditional dread of syphilis that exists to this day, but perhaps much of that may have been due to misuse in the past of the available remedies. My personal knowledge of the effect of pre-Salvarsan remedies on syphilis was not great but sufficient to make me certain that if they had remained the only stand-by nothing would have stayed my persistence in efforts to get out of this branch of medicine at the earliest possible moment, such seemed to be the heart-breaking results of one's most earnest care in treatment.

To particularize, as a student I saw mostly cases of late syphilis; the statutes of most hospitals in Great

Britain preventing them then from admitting patients with early syphilis. There were plenty of late cases, however, providing a rich material for teaching purposes, and the phrase “when in doubt, play iodide” might have been regarded as a medical cliché. At the Royal Victoria Hospital, Netley, which I visited in the early '90s as a member of the Volunteer Medical Staff Corps, I saw a wardful of soldiers whose faces were rotting away from the effects of tertiary syphilis, excellent material for the wax models of the horrors of syphilis which some Continental towns included in their museums by way of trying to keep their people in the path of sexual virtue, and a reminder of what earlier writers seem to have regarded as the classical effect of syphilis if one may judge by Addison's “Essay on Noses”.

At the Military Hospital, Rochester Row, an old Guards' hospital which that earnest pioneer for the systematic treatment of syphilis in the army, the late Col. F. J. Lambkin, had persuaded the War Office to allocate to the treatment of, and instruction in, venereal diseases, I had the opportunity, from the autumn of 1909 to the summer of 1910, of seeing the defects of what was then considered the latest in the treatment of syphilis. So far as the regular injection of mercurial suspensions was concerned, the results seemed to me heart-breaking. In too many cases a dosage short of that causing salivation left the patient a prey to frequent relapse even during a course of treatment. Thus in the first year of early syphilis treated with perfect regularity at Rochester Row, the syphilis case-records of 378 Guards patients which I examined at a later date showed an average of 42 days spent in hospital in the first instance and a total of more than 500 clinical relapses requiring re-admission to hospital. At that time the official treatment of syphilis in the army required regular courses of injections of mercurial cream, with rest intervals spread over a period of at least 2 years. In France, as I understood from discussions at that time, it was considered that the minimum period of treatment should be 4 years, and it was interesting to me to be told by a retired

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regimental medical officer that he had always kept his syphilitic patients under treatment by mercury pills for at least 3 years. He said it was pleasing to see how in the third year the patients again began to look healthy. A strong scepticism of the curative value of mercury soon made me plan a systematic serum test of soldiers 3 months after they had undergone the standard 2 years' treatment of early syphilis. Much later I found that 42 per cent. of these men were still positive to the Wassermann test of that day, a much less sensitive one than it was made later, and that over 75 per cent. were positive to the modification made by Marguerite Stern (1909), which used the natural complement in fresh human serum and was nearly 100 per cent. specific.

Some of the patients at Rochester Row were still being treated by some pentavalent arsenical preparations, viz. Atoxyl (Soamin here), arsacetin, and atoxylate of mercury, and in a pretty large series of cases which Lambkin had treated before I joined I found a surprisingly large percentage of negative serums. Elsewhere, the toxic effects of these arsenical preparations had been reported to have caused blindness from retro-bulbar neuritis, and by the end of 1909, Lambkin having left, they had mostly been discarded.

So much for the bad old pre-Salvarsan days. The good effect of atoxyl on trypanosomiasis demonstrated by Thomas (Liverpool) and the relationship which Schaudinn, the discoverer of *T. pallidum*, believed to exist between this organism and trypanosomes doubtless led Ehrlich to re-examine the chemical formula of atoxyl and eventually, in association with Bertheim against the scepticism of other colleagues in the Georg-Speyer Haus, to establish the fact that atoxyl was not an anilide of arsenic acid as believed by Béchamp, its discoverer in 1863, but contained a free amino group which made the synthesis of derivatives possible. This discovery led to the long series of experiments ending in the synthesis of "606". It may also be interesting to know that, according to Martha Marquardt, whose fascinating biography of Ehrlich ought to be read by every venereologist, "606" might not have been put to clinical trial if its effects on spirochaetosis had not been re-tested in Ehrlich's laboratory by his Japanese disciple, Hata, because a predecessor of the latter had reported unfavourably on it.

The first clinical trials of "606" were reported to the Medical Society of Magdeburg on March 3, 1910, by K. Alt, and later published in the *Münchener medizinische Wochenschrift*, under the title "Das neueste Ehrlich-Hatapräparat gegen Syphilis". The adjective "neueste" was used because of a previous trial by Alt of an earlier trivalent arsenical remedy

called "Arsenophenylglycin" ("418" or "Spirarsyl"), a sample of which had been given to Lambkin but had not been tried by him; fortunately so because it was too toxic. Alt's report and others which quickly followed naturally excited the liveliest interest and a flood of requests for samples. We learnt that Ehrlich would not have the drug placed on the market until it had been sufficiently tested in clinics well equipped for observation of its effects, and, in fact, it was not until 8 months after the publication of Alt's paper and about 40,000 doses had been distributed to approved clinics, that "606" appeared on the market as "Salvarsan". In our application for samples we pointed out that we were in a very favourable position for observation of the drug's effects since our patients were under military control and we could follow them up at any rate until they left the army. In fulfilment of the undertaking contained in our application, we persuaded the War Office to issue a directive that whenever we asked for a sample of a soldier's blood, it was to be sent to Rochester Row from wherever the soldier was stationed. Thus from that time until August, 1914, we acquired information about Salvarsan which was immensely helpful to me in framing courses of treatment for soldiers who became infected with syphilis in the war of 1914-18. Also we had reason to believe that our reports were useful to Ehrlich and his colleagues at the Georg-Speyer Haus before and after Salvarsan could be bought.

Our request for samples had a generous response and we continued to receive fresh batches until October, 1910. The administration of the first dose at Rochester Row is for me an indelible memory. Between the date of our application for samples and their arrival I had earnestly studied all the literature I could find on the technique of preparation, dosage, administration, and so forth and, being a poor German scholar, faced with the knowledge that in the dose to be given would be over thirty times as much arsenic as is contained in the top dose of arsenious oxide, there was much anxious study and re-study of technique. We chose the method recommended by Wechsellmann (1910) in which the drug was first dissolved by rubbing it up with 1 to 2 ml. sodium hydrate solution, then precipitated to a fine yellow mud by cautious addition of glacial acetic acid, suspended in 1 to 2 ml. distilled water, and neutralized to litmus. It was injected under the fat of the inter-scapular area. That evening the patient's temperature was 104° F. and he was in agony. I gave him a big dose of morphia and judged that I had better call on my commanding officer and tell him about it. We concluded that in any case we couldn't extract the dose, and that many similar

doses must have been given elsewhere by the same technique, and the only further thing I thought I could do was, myself, to take a good hypnotic to prevent the nocturnal tossing and turning which the thought of that patient seemed likely to excite. Next morning the patient's temperature was normal but his syphilitic signs were more marked (my introduction to the Jarisch-Herxheimer reaction); by evening, however, there was such an improvement in the signs of syphilis as none of us had ever seen in acute syphilis in so short a time.

With that and similar experiences in therapeutic effect we had reason to hope that Ehrlich had achieved his ambition to construct a *therapia sterilisans magna*. But clinical relapses began to appear in the course of weeks to show us that more than one dose was necessary for the cure of syphilis. It soon became clear also that the value of "606" would be only slight if it had to be given into the tissues because few would be persuaded to endure the agony of further injections. It was a great relief therefore to learn from an article by Schreiber and Hoppe (1910), a few weeks after the start of our investigation, that "606" could be given intravenously. So we imported the apparatus used by Schreiber, a syringe with a two-way tap by means of which it could be filled repeatedly with the remedy from a container and then emptied into the vein, the needle remaining *in situ* throughout the injection of about 250 ml. fluid. The Schreiber apparatus was decidedly not a convenient one for intravenous injection; the connection between the needle and the syringe was rigid and what with fear of the needle being displaced in the repeated turning of the tap and filling of the syringe, and fear of air getting into the system, each injection was a very tiring business.

It may not be out of place to tell here how what became known as the Rochester Row apparatus for injection of "606" came to be invented. An officer working in the Queen Alexandra Military Hospital, Millbank, asked me to give one of his patients, an early case of general paralysis of the insane, an injection of "606", so I asked permission to take the Schreiber apparatus over to Millbank for the purpose. Permission was refused and this frustration engendered the thought that, after all, one did not need a syringe to get solution into a vein; in the hospital's equipment was an item known, I think, as Horrocks's transfusion apparatus, which consisted of a small glass funnel like the barrel of an ordinary glass ear-syringe, but with a capacity of only about an ounce, attached to which was about three feet of rubber tubing and at the lower end a connexion for the needle. So we sterilized this outfit and, having filled it with saline, I inserted the needle into

the vein. After this it was a matter of repeatedly filling the glass funnel with the prepared "606" solution and milking it down the tubing. At one time during this performance the patient reached over with the injected arm to scratch his other arm but to my great relief the needle was not disturbed. After this experience we discarded the Schreiber syringe and gave all our doses by gravity. The finished model consisted of a cylindrical funnel of about 250 ml. capacity to hold the "606" solution, another alongside it for saline, to precede and follow the "606" into the vein, the rubber tube from each of these funnels being connected to one arm of a Y-piece, the leg of which was connected through rubber tubing to the needle connexion. A few modifications during the first few weeks of its use led to the model which was used in the army and in a number of clinics elsewhere so long as Salvarsan continued to be used, *i.e.* until at least 1919.

The clinical relapses elsewhere excited criticism of the remedy which must have troubled the staff at the Georg-Speyer Haus, but by then I had seen too much of what seemed to me the almost miraculous disappearance of *T. pallidum* from the juice of early lesions, as also the effect on the serum reactions—we tested patients' blood every week for a number of months after giving the first dose—not to feel that here was no merely symptomatic remedy. The Vienna School might criticise to their heart's content; we felt that here was a remedy which would change the prospects out of recognition for every patient with early syphilis. Our governing thought was how to make the best use of Ehrlich's discovery, and we aimed to learn (a) the minimum total dose of "606" necessary to cure an average case of early syphilis and (b) how to avoid killing the patient with haemorrhagic encephalopathy, a side-effect of the new therapy which soon began to be reported in the literature.

The first of these objectives seemed likely to be achieved by giving to successive series of patients more and more of the arsenical remedy, which after a very short time we began to combine with mercurial treatment as recommended by Neisser. As regards the second, a close study of the reports on deaths from encephalopathy disclosed none in which the interval between full doses of "606" had been 2 weeks or more. Accordingly in all pre-war work at Rochester Row a rule of not less than 2 weeks between *full* doses was observed and we had no case of the kind.

Another untoward result of Salvarsan therapy, which, one would judge from biographies of Ehrlich, must have caused him great anxiety, was the occurrence of cranial nerve palsies and other

lesions of the central nervous system which stimulated in the Vienna and some other schools the criticism that these happenings were evidence of a neurotropic effect of the arsenical remedies. We who saw no such occurrence in the patients we treated with these remedies had no hesitation in agreeing with the Frankfort staff that cranial nerve palsies were evidence of syphilitic recurrence. We attributed our freedom from this kind of trouble to the fact that from a very early date in our trials of the remedy, we had simultaneously given mercury. To enter into the arguments pro and con the concurrent use of heavy metal with arsphenamines would spin this paper out interminably and I will say here only that later evidence has convincingly supported my view that, although I have seen cases of well-proven syphilis which (judging by thorough tests many years later) have apparently been cured by a single full dose of Salvarsan, by and large, the arsphenamines are not a complete treatment of syphilis and should be given *concurrently* with heavy metal.

In the above account of our early experiences with Salvarsan, I have made no mention of Neosalvarsan, which was issued in 1912 as an improvement in respect of safety and convenience on Salvarsan. In respect of safety and convenience, my small experience of Neosalvarsan before 1914 supported these claims, but at Rochester Row we stuck mainly to the older remedy because we believed that it was more effective therapeutically, and throughout the war of 1914-18, whenever I had anything to do with the treatment of syphilis, I did my best (sometimes at expense of great trouble) to give Salvarsan. In our preference, we were in agreement with the naval surgeon, Gennerich, whose work in this field at Kiel must have been invaluable to Ehrlich.

Thus I hope I have shown that, after due test, we at the Rochester Row Hospital accepted Ehrlich's remedies with gratitude, and, far from criticizing them in the carping spirit shown in, I am glad to say, only a small minority of the articles on this subject, we sought to make the best of what we regarded as an advance in the treatment of syphilis for which mankind should be forever grateful.

The benefits which have accrued from the addition of Ehrlich's remedies to our armamentarium for the treatment of syphilis are not easy to assess with any accuracy, because of intervening factors such as the two wars (with invasion of these islands by friendly allies, which must have increased the incidence of syphilis), and the treatment of neurosyphilis with fever-producing agents, which is a material factor in the great reduction of mortality at least from G.P.I. Altogether I feel that to enter into this side

of the question at any length would engender controversy, besides exceeding the limits which must be put on an article of this nature. I must therefore confine myself to a few facts on which I think there can be general agreement so far as Great Britain is concerned.

The evidence which we collected at Rochester Row caused the Government at long last to appoint the Royal Commission on Venereal Diseases for which earnest workers had been pressing for many years. This led to the institution of the V.D. Scheme, because it was believed by the Royal Commission that the spread of syphilis could be prevented by making as high a proportion as possible of the infected in the population quickly non-contagious with Salvarsan. At the outbreak of the war of 1939-45 the number of cases of syphilis of less than one year's duration dealt with for the first time in civilian clinics in England and Wales was less than 5,000; I calculate that the number of similar cases in 1920 was more than three times this number. In various reports in the past I have given reason for believing that from the early 1920s the venereal diseases treatment centres dealt with the overwhelming majority of fresh infections with syphilis in England and Wales, and that the steady fall in cases of acquired syphilis with infections of less than one year listed separately in the Annual Report of the Chief Medical Officer, Ministry of Health, from 1931 (when the total was 9,104) to 1939 (when it was 4,896), represented a true fall in the incidence of syphilitic infection in England and Wales for which Ehrlich's arsenical preparations were largely responsible. Some scepticism of the view respecting incidence was expressed when a statement to this effect was made some time before the war broke out, and it was then suggested that there was much hidden syphilis in the rural areas. This suggestion was refuted by the fact that infections of service men in rural areas were negligible during the first year or so of the war, if one may believe the Tables stating the localities of their infections which were kindly sent to me monthly by service medical officers. Parenthetically, it may be mentioned that after 1939 the figures rose almost steadily to a peak in 1946, when the numbers were 10,705 males and 6,970 females. The rise in incidence during the war of 1939-45 demonstrated by these figures supports what is said below about the probable rise during the war of 1914-18, and about the effect of the arsenical treatment of syphilitic soldiers in preventing such late effects as aneurysm.

Another significant figure has been the infant mortality rate certified as due to syphilis. In 1912 this rate was 1.34 per 1,000 live births; it rose to a

peak of 2.03 in 1917 and thereafter it fell almost steadily until in 1944, before any effect of penicillin can have been a factor, it was 0.16.

The question of the influence of the arsphenamines on late effects of syphilis is complicated by various factors. It is tempting to claim some of the credit for the fall in deaths from G.P.I. in England and Wales from an average of 1,697 males and 383 females per annum in the decade 1911 to 1920 to an average of 482 and 167 in the five years 1940 to 1944, but we do not know the influence of fever treatment and possibly of tryparsamide in preventing even admissions to mental hospitals. Certainly treatment in the early stages 20 years previously must have had its effect. In cardiovascular syphilis we may be on safer ground. In the literature there is good evidence that adequate treatment in the early stages was strongly preventive of cardiovascular syphilis, and indirect evidence to the same effect may be seen in the Registrar-General's statistics relating to aneurysm from 1911 to 1937, particularly so in the differences between the figures for males and those for females in respect of changes in incidence of these deaths. In 1911 the deaths certified as due to aneurysm in England and Wales were 935 males and 225 females. In the war of 1914-18 we know that approximately 100,000 British soldiers were treated for syphilis, mostly of course in the early stages, suggesting a great increase in the incidence of syphilis in the country, an increase that must have affected females as well as males; this can be inferred from the figures quoted above respecting increases that occurred in the numbers of cases dealt with in the civilian treatment centres during the war of 1939-45. Such an increase in infections as must have occurred during the war of 1914-18 would be expected to be reflected in the figures relating to deaths from aneurysm 20 years or so later. But

soldiers infected during the war of 1914-18 were mostly treated with arsenical and mercurial remedies, while females, the V.D. Scheme being then in its infancy, must have gone largely untreated. In 1937 the number of males certified as having died from aneurysm was 1,001, while the number of females was 538. In other words, there was only a slight increase over the 1911 figure in the male deaths and a very big increase in the female deaths. It is a fair inference that the treatment given to syphilitic soldiers during the war of 1914-18 was very effective in preventing late effects, and for this the credit is largely due to Ehrlich's arsphenamines.

I had the honour of meeting Ehrlich only once, in 1913 during the International Medical Congress in London. He impressed me as an unassuming but very earnest man. Many years later I was glad to find this impression confirmed in his secretary's biography and I do not think I can conclude better than by quoting the penultimate paragraph of my review, in this journal, of Miss Marquardt's book :

"One great feature I have not emphasized sufficiently which is well brought out by Miss Marquardt : it was Ehrlich's simplicity and lack of any kind of pomposity or professorial demeanour. When one thinks of the unassuming great men with whom we have been blessed in the past century, one could wish that the strutters, the jacks-in-office, and the like could be made to study such biographies as this, that they might learn how the really great comport themselves."

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